REMARKS

The continuing data has been inserted into the specification and therefore the objection thereto can now be withdrawn.

The syntax of claim 12 has been revised as suggested by the Examiner. The change does not alter the scope of this claim. Because claims 13 and 14 referred to the liquid pharmaceutical formulation of claims 11 and 12 and those were process claims, an appropriate correction has been made to make these claims refer to claims 1 and 8. Accordingly, it is respectfully submitted the rejection under § 112 can be withdrawn.

The indication of allowable of claims 8, 12 and 15 is again noted with appreciation.

Reconsideration of the rejection of claims 1, 3, 7, 9 and 10 under 35 U.S.C. § 103 over Hanisch in view of Hershenson and of claims 4, 6, 11 and 14 under 35 U.S.C. § 103 over Hanisch in view of Hershenson and Cymbalista.

In connection with the following remarks, the Examiner's attention is respectfully invited into the Declaration of Mark C. Manning which is attached to this response.

The Office Action acknowledges that a liquid composition containing certain specific amounts of interferon-beta, mannitol and albumin in an acetate buffer is novel and unobvious. The rejected claims define the amount in somewhat broader form. It is respectfully submitted that these other claims are likewise patentable.

The principle reference, Hanisch, relates to purifying and processing two recombinant proteins, namely human interferon-beta and interleukin-2, in order to produce a composition in which the recombinant protein is dissolved in a non-toxic,

therapeutically compatible, aqueous-based carrier at a pH of 6.8 to 7.5. In one of the procedures described there is at one stage of the process a low pH (2-4) solution which contains neither a stabilizer nor a buffer. If desired, the low pH solution can be lyophilized and when lyophilized, a carbohydrate stabilizer such as dextrose or mannitol can be added. As pointed out by Professor Manning, carbohydrates act on a lyophilized formulation by a vastly different mechanism then they function in a liquid formulation. In a lyophilized carbonation, the carbohydrates replace the water removed by freeze drying whereas in a liquid formulation, they act as an excluded solute, thereby increasing the thermodynamic stability of the protein in solution. The claims in this application do not relate to a lyophilized formulation.

The Office Action acknowledges that Hanisch does not teach the use of a buffer in a pharmaceutical composition and then attempts to overcome this deficiency by advancing several contentions. First, it avers that a person skilled in the art would "immediately envision" the use of a buffer in the preparation of a pharmaceutical composition and it also would have been obvious to use the buffer to maintain the pH, especially if the pharmaceutical composition was to be stored. If is respectfully submitted that the first of these assertions ("immediately envision") is an assertion made without any factual basis and is an attempt to justify the rejection through the use of hindsight. The second part of this assertion (use a buffer to maintain the pH, especially if the composition is to be stored) likewise lacks a factual basis in that it necessarily assumes that something must be added to maintain the pH of the solution whereas there is nothing in the Hanisch reference which indicates that there is any problem in maintaining the pH of the solution. The assertion in the Office Action that any liquid pharmaceutical composition "must be buffered" likewise lacks a factual basis and there are numerous liquid compositions which are stored, shipped and sold

without being buffered. The further assertion that it would be obvious to re-suspend a lyophilized material using a buffer also lacks a factual basis.

Because of a lack of a factual basis, all of these assertions must be based on "common knowledge" or "basic knowledge" in the art, even though those words are not found in the Office Action. Any such reliance is improper. *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002)

Beyond the foregoing deficiencies, and as pointed out by Professor Manning, proteins are polyelectrolyte that can buffer solutions themselves, thereby obviating the need for a buffer system to maintain a pH as presumed in the rejection, and given the large pH changes during the processing described by the Hanisch patent, use of a buffer would be problematic because that would require numerous buffer exchanges as the pH desired in the various stages was achieved.

A number of pharmaceutical compositions do, of course, employ buffers and therefore the citation of any particular reference for the proposition that it is theoretically possible to employ a buffer would not add any additional teaching to the substance of the rejection. In the first instance, there would have to be motivation to combine that additional reference with Hanisch, particularly in view of the considerations set forth in the paragraph immediate above. Motivation is absent in any proposed combination applied to the instant claims. Then, any such reference would have to be evaluated in the context of what it actually teaches about a composition containing a buffer. In the latter connection, while the Herschenson reference does teach a interferon composition containing a buffer, it also teaches that either glycerol or PEG polymers must be present, neither of which are included in the instant claims, and it further teaches that the buffers used are phosphoric acid, glycine and citric acid or, more preferably, phosphate. Acetate buffers are neither taught nor suggested. While

the Office Action avers that Herschenson does not teach that the glycerol or PEG polymers are required, this assertion is respectfully submitted to be a hindsight reinterpretation of what is disclosed. As Professor Manning points out, all of the buffered materials in the references contain glycerol or PEG.

The Cymbalista patent, which has been cited only against some of the claims, does teach an acetate buffer but only when used in combination with PVP as a stabilizer. There is nothing in the reference that shows an acetate buffer would give any degree of stabilization in the absence of PVP, even assuming that the use of a buffer was not contrary to the teachings of Hanisch, which it is.

Beyond all of the foregoing, Hanisch teaches that the type of stabilizer employed will depend mainly on the pH method and formulation employed and on the protein. Col. 9, lines 37-39. Albumin is preferred for high pH formulations or formulations where the protein is interlukin-2. Col. 9, lines 39-43. "However, for a low pH formulations using [interferon-beta], PPF is preferred." *Id.* at lines 43-44. As the Office Action points out, PPF is composed of at least 83% albumin and necessarily contains other materials. The use of a material which contains fractions other than albumin is thus not preferred for any low pH interferon-beta composition. It is respectfully submitted that it is clear that an (improper) hindsight approach to obviousness is being employed when it is realized that the rejection require one to employ an optional material and then select a non- preferred material as that optional material, and further to add a buffer which the reference does not indicate is desired.

While various bits and pieces of the claimed invention can be found in the three (3) references which are relied on in the Office Action, nothing in any of these references teach or suggest the selection and combination of the particular materials recited in the instant claims. The selections proposed in the Office Action require the

use of hindsight without any motivation to do so, and that is not permissible. These considerations are reinforced by the Declaration of Dr. Esposito, which is already of record and the Declaration of Professor Manning submitted herewith.

Beyond the foregoing, the data in the application shows that the claimed combination gives surprising and unexpected results. This is detailed in the Declaration of Professor Manning. See, e.g., *In re Soni*, 34 USPQ2d 1685 (Fed. Cir. 1995)(showing of substantially improved results and a statement that results were unexpected "suffices to established unexpected results absent evident to the contrary.") It is also respectfully submitted that the attempt to ignore the surprising and unexpected results on the grounds that the claims do not require a particular degree of stabilization is improper. That justification might be appropriate if the claims were directed to a method of stabilizing but the instant claims are directed to a composition and method of making the composition. The degree of stabilization is a property of the formulation itself. The fact that the claimed composition has an outstanding degree of stabilization compared to formulations which are even closer to the invention than in any of the cited art is surprising and expected and this characteristic alone would render the claimed invention patentable.

In light of all of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited.

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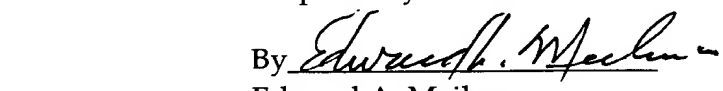
Respectfully submitted,

By 

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